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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,630	10/29/2001	Philip C. Wong	JHU1690-2	6218
7590	07/12/2004			
Gray Cary Ware & Freidenrich LLP Suite 1100 4365 Executive Drive San Diego, CA 92121-2133			EXAMINER BERTOGIJO, VALARIE E	
			ART UNIT 1632	PAPER NUMBER

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/003,630	WONG ET AL.
	Examiner Valarie Bertoglio	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 19 May 2004.
- 2a) This action is **FINAL**.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-34,37 and 40-57 is/are pending in the application.
- 4a) Of the above claim(s) 1-33 and 40-56 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 34,37,40 and 57 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 10/29/2001 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____.
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____.

## **DETAILED ACTION**

Applicant's amendment filed 05/19/2004 has been entered. Claims 34,37 and 40 have been amended. Claim 57 has been added. Claims 1-33 and 41-56 are withdrawn as being drawn to a non-elected invention. Claims 35-36 and 38-39 have been cancelled. Claims 1-34,37 and 40-57 are pending and claims 34,37,40 and 57 are currently under consideration.

### ***Election/Restrictions***

Applicant elected Group XVIII without traverse in the election dated 08/08/2003. As set forth in the action mailed 10/03/2003, the elected invention is drawn to a method for identifying an agent that modulates the expression or activity of BACE1 by comparing the phenotype of a transgenic A $\beta$ 1-42 organism contacted with the agent to that of a BACE-1 knockout organism. The amendment received 02/05/2004 was non-responsive as the amended claims were drawn the non-elected invention Group XIV which is drawn to a method for identifying an agent that modulates the expression or activity of BACE1 by comparing the phenotype of a wildtype organism contacted with the agent to that of a BACE-1 knockout organism. Claims are currently amended to read on elected Group XVIII, however, it is noted that Applicant recites on page 9, last paragraph, of the response filed 05/19/2004, currently under consideration, that the amended claims read on elected Group XIV. This is considered to be a typographical error as the amended claims no longer read on Group XIV, but read properly on elected Group XVIII.

### ***Oath/Declaration***

The oath submitted 04/11/2002 is proper. The boxed checked on PTO form 326 mailed 10/03/2003, indicating that the oath is improper, was done so in error.

***Claim Objections***

The objection to the claims as being drawn to a non-elected invention is withdrawn.

***Information Disclosure Statement***

Applicant has requested consideration of an IDS mailed April 09, 2003. No IDS other than that received by the office 09/16/2002 is of record. It is requested that Applicant resubmit the IDS mailed April 09, 2003, including the mailing receipt indicating the initial date of mailing.

***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written Description***

The rejection of claims 34-40 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of Applicant's amendments to the claims.

*Enablement*

Claims 34,37,40 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments and amendments have been thoroughly considered and are partially persuasive.

Claims are drawn to a method for identifying an agent that modulates the expression or activity of BACE1 comprising administering an agent to transgenic mouse comprising a transgene causing overexpression of A $\beta$ 1-42 and comparing the phenotype of the said transgenic mouse to that of a BACE-1 knockout mouse not contacted with the agent, whereby a phenotype in the transgenic A $\beta$ 1-42 mouse substantially equal to the BACE-1 knockout mouse is indicative of an agent that modulates BACE-1 activity.

The specification describes generating a BACE1 knockout mouse by targeted gene insertion into the mouse BACE-1 gene. The specification teaches that the mouse lacks the APP cleavage products A $\beta$ 1-40/42 and A $\beta$ 11-40/42. The specification contemplates that the BACE-1 knockout mouse can be used as a control, or baseline, for comparison with mice expressing BACE-1 that have been treated with an agent that is a candidate for having BACE-1 modulatory activity (page 5, last paragraph). This assay is based on the premise that if the agent suppresses BACE-1 expression or activity in an organism that normally expresses BACE-1, then that organism will phenotypically resemble the BACE-1 knockout organism.

As the claims are now limited to mice, the rejection on the grounds that the specification is not enabling for any species of organism is withdrawn.

The aspect of the rejection based on the breadth of the claims with respect to symptoms associated with Alzheimer's disease (page 10 of previous office action mailed 10/03/2003) is withdrawn in light of Applicant's amendments.

The rejection based on the grounds that the specification fails to teach an A $\beta$ 1-42 transgenic organism is maintained (refer to page 9 of the office action mailed 10/03/2003). While Applicant has limited the breadth of the organism species claimed to mouse, the specification fails to enable the claimed A $\beta$ 1-42 transgenic mouse as previously rejected. Applicant has argued in response to this rejection as though it pertains to the BACE-1 knockout mouse also encompassed by the claims. The rejection, however, is not directed to the BACE-1 knockout mouse but to the A $\beta$ 1-42 transgenic mouse. Therefore, the rejection is maintained for reasons of record set forth on page 9 of the office action mailed 10/03/2003.

Applicant failed to respond to the aspect of the rejection on the grounds that the specification fails to enable the claimed methods broadly encompassing agents that both increase and decrease BACE1 activity. Thus, this aspect of the rejection is maintained for reasons of record set forth on page 10, paragraph 2, of the office action mailed 10/03/2003.

The specification fails to enable making and using the A $\beta$ 1-42 transgenic mice as encompassed by the newly amended claims. The claims as amended encompass a method of identifying an agent that modulates BACE-1 by treating, with a candidate BACE-1 modulatory agent, a transgenic mouse overexpressing A $\beta$ 1-42 and comparing levels of A $\beta$ 1-42 to those of an untreated BACE-1 knockout mouse, which as taught by the specification would fail to secrete A $\beta$ 1-42. The premise is that the transgene would cause elevated A $\beta$ 1-42 and a compound that results in phenocopying the levels of A $\beta$ 1-42 production in the BACE-1 knockout would be a

compound that not only eliminates endogenous BACE-1 mediated A $\beta$ 1-42 formation but also A $\beta$ 1-42 expressed from the transgene. The caveat to this logic is that the agent being identified modulates expression or activity of BACE-1. If A $\beta$ 1-42 is being expressed under the control of a promoter that is independent of BACE-1, a BACE-1 regulatory agent will not effect A $\beta$ 1-42 expression from the transgene. Thus, in effect, a BACE-1 inhibitor may not be identified using the claimed methods because A $\beta$ 1-42 is present in the mouse as a result of transgene expression despite inhibition of BACE-1 expression or activity. The specification does not teach how to make the claimed A $\beta$ 1-42 transgenic mice such that an inhibitor of BACE-1 expression or activity would affect the A $\beta$ 1-42 expression from the transgene or such that lack of A $\beta$ 1-42 expression from the transgene would be indicative of a BACE-1 modulator. Therefore, in light of the lack of guidance in the specification with respect to how to make the A $\beta$ 1-42 transgenic mouse, one of skill in the art would not know how to use an A $\beta$ 1-42 transgenic mouse to screen for compounds that phenocopy the level of A $\beta$ 1-42 production in a BACE-1 knockout mouse.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34,37,40 and newly added claim 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has argued that the phrase "substantially equal" in claim 34 is not indefinite based on the decision upholding such

phraseology in Deering Precision Instruments L.L.C. v. Vector Distribution Systems Inc, CAFC, 10/17/03; USPQ2d, Vol. 68, No. 7, 1716).

According to the above-cited U.S. Court of Appeals decision, the term “substantially” can be interpreted in a multitude of ways. In the case at hand, the court determined that the specification provided sufficient teachings within the context of the invention that the metes and bounds of the term “substantially” could be determined. In the instant case, the specification does not provide such teachings and it is, therefore, unclear what levels of A $\beta$ 1-42 in the treated transgenic mouse would be substantially equal to that of the BACE1 knockout mouse. As such, the rejection is maintained for claims 34,37,40 and 57.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
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Art Unit 1632  
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